B1

PATENT SPECIFICATION

NO DRAWINGS

874,586

Date of Application and filing Complete Specification: Aug 21, 1958.

No. 26940/58.

Application made in United States of America on Oct. 28, 1957.

Complete Specification Published: Aug. 10, 1961.

Index at acceptance:—Class 81(1), B(2C: 2G: 2R1: 2S: 2Z: 3: 4: 6).

International Classification:—A61k.

COMPLETE SPECIFICATION

Improvements in or relating to Therapeutic Compositions and the manufacture thereof

We, THE UPJOHN COMPANY, a corporation organized and existing under the laws of the State of Delaware, United States of America, of 301 Henrietta Street, Kalamazoo, State of Michigan, United States of America, do hereby declare the invention, for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement:—

This invention relates to a medicinal tablet and to a process for its production and more particularly relates to a tablet containing an adrenocortical steroid hormone, calcium carbonate and acetylsalicylic acid in a special stable form and to a process for the production of such a tablet.

Adrenocortical steroid hormones are now well-established therapeutic agents having a wide range of applications in the medical field. Cortisone, hydrocortisone and their more recently introduced analogues, for example, prednisone, prednisolone, and 6-methyl-prednisolone, have been found especially useful as systemic and topical anti-inflammatory agents. Thus, they have been used in the treatment of rheumatic diseases and allergies.

Acetylsalicylic acid, i.e. aspirin, is probably one of the best known of all therapeutic agents. Its usefulness extends all the way from treating simple headaches to treating such disabling diseases as rheumatism.

It is largely because both the corticosteroids and aspirin are useful in treating rheumatic diseases that it has been thought desirable to combine the two ingredients, particularly in an oral dosage form which is the most convenient form for administering the two drugs. Since both ingredients sometimes cause gastrointestinal upsets when taken orally, it would also be desirable to include a buffer in such an oral dosage form.

However, the actual preparation of such an oral dosage form presented unusual and unexpected difficulties. Thus, when a simple compressed tablet, capsule or bulk powders of the above ingredients are prepared, the hormone is partially oxidized, the aspirin hydrolyzed, the buffer neutralized and a heavy gas pressure developed.

It is therefore an object of this invention to provide a pharmaceutically elegant buffered medicinal tablet containing an adrenocortical steroid hormone and acetylsalicylic acid. Other objects of the invention will be apparent to those skilled in the art to which this invention pertains.

The foregoing and additional objects have been accomplished by the provision of a compression-coated medicinal tablet comprising an inner core section containing a mixture of an adrenocortical steroid hormone and calcium carbonate and an outer layer surrounding said core section containing acetylsalicylic acid or a non-toxic compound yielding acetylsalicylic acid on hydrolysis. Such a tablet is prepared by a novel process comprising the addition of a powdered adrenocortical steroid hormone to previously granulated calcium carbonate, compressing the adrenocortical steroid hormone-calcium carbonate mixture to form the core section of the ultimate tablet, and surrounding said core section with a bonded layer containing the acetylsalicylic compound. These steps should preferably be carried out under low humidity conditions with dried ingredients to provide a tablet having a water content of less than 0.9 percent by weight. A tablet prepared by such a process possesses greater chemical stability of the hormone, greater chemical stability of the acetylsalicylic acid, greater buffer activity, greater physical stability, faster disintegration characteristics, and greater all-around pharmaceutical elegance than similar products available heretofore. Moreover, such a tablet has favorable size characteristics and lends itself easily to practical manufacturing requirements.

The term "adrenocortical steroid hormone" as used herein has reference to steroids of the adrenal cortex, e.g. cortisone and hydrocortisone and their therapeutically active deriva-

[*Price 3s. 6d.*]

Price 5s. 0d.

tives and analogues. Typical derivatives include esters and ethers, especially the acetate ester. Typical analogues include prednisone, prednisolone, 6-methyl-prednisone, 6-methyl-prednisolone, 6-fluoro-hydrocortisone and 6-fluoro-prednisolone. Derivatives of such analogues, e.g. the acetate ester, are also included.

The term "compression-coated" as used herein has reference to the method described in Remington, Practice of Pharmacy, Eleventh Edition, page 406, Mack Publishing Company, 1956.

Prior to the present invention it was not known how a stable composition containing an adrenocortical steroid hormone, an acetylsalicylic acid compound and calcium carbonate could be prepared. If all of the ingredients were intimately mixed or compressed as a single mixture, the acetylsalicylic acid would undergo hydrolysis with the production of undesirable acetic acid odor, salicylic acid formation and a pink coloration. Thus, when such a powder mixture containing 200 milligrams of calcium carbonate and 300 milligrams of acetylsalicylic acid was prepared, the acetylsalicylic acid underwent 7.38 percent hydrolysis after one year at room temperature, (Method of analysis: Tinker and Mc Bay, J.A.Ph. Assoc., Scientific Edition, 43, page 315, 1954). Such degradation is tremendously excessive as evidenced by the fact that the U.S.P. limit for hydrolysis in acetylsalicylic acid tablets is only 0.15 percent. A simple compressed tablet of the above ingredients is even less stable since the hormone is partially oxidized, the aspirin hydrolyzed, the buffer neutralized (by liberated acetic acid) and a heavy gas pressure developed (by reaction of liberated acetic acid with calcium carbonate).

When the problem was first encountered, many procedures and dosage forms and combinations thereof were tried, but only the medicinal tablet and process of this invention satisfied all of the therapeutic and manufacturing requirements for a suitable commercial product. These requirements relate to ease of manufacture, stability of the active ingredients, size of finished dosage form, pharmaceutical elegance, and the like.

The arrangement of the active ingredients in the compression-coated tablet is critical. It is possible to arrange the three active ingredients in the ultimate tablet in several different ways. The present invention comprising a core containing the steroid and calcium carbonate and a compression-coat containing the acetylsalicylic acid compound has been found to be superior to the other possible arrangements because it meets satisfactorily the various problems concerned, i.e., ease of manufacture, size of the ultimate tablet, pharmaceutical elegance, buffering capacity, stability of the active ingredients, and the like.

For the preparation of the core component of the ultimate tablet, there is first prepared a granulation of calcium carbonate in the usual manner. The powdered steroid is then mixed into and blended with the calcium carbonate granulation. This admixture of steroid and calcium carbonate is compressed to form the tablet core. Subsequently, said tablet core is coated uniformly with the acetylsalicylic acid compound by the technique known in the art as compression-coating. This technique comprises controlled feeding to a compressing machine of the lower granulation charge of the acetylsalicylic acid compound, perfect centering of the tablet core on and within the lower charge, controlled feeding of the upper granulation charge of the acetylsalicylic compound, and compressing simultaneously the lower and upper granulation charges around the tablet core. Precautions are exercised to maintain the moisture content of all ingredients, and the humidity of the surrounding atmosphere, at low levels consistent with maximum stability.

The active ingredients in the ultimate compression-coated tablet can be varied over a range consistent with the practical limitations of oral tablet size and in harmony with the pertinent therapeutic indications. The usual dosage of acetylsalicylic acid, i.e. about 300 milligrams is preferred. However, from 200 to 400 milligrams can be utilized. The requirement of calcium carbonate is related to the amount of acetylsalicylic acid. Said requirement is met by an amount of calcium carbonate at least equimolar with the acetylsalicylic acid. It is preferred, however, to use more than the equimolar amount of calcium carbonate by about 100 milligrams to ensure neutralization and buffering of the gastric contents which are known to be normally acidic with a pH of approximately 1.0. The amount of adrenocortical hormone can vary from 0.15 to 10 milligrams.

Various supplementary and complementary active ingredients can be added to the composition of this invention. Muscle relaxants or tranquilizers, for example, meprobamate, 50 to 200 milligrams, reserpine, 0.25 to 1 milligram; analgesics, for example, codeine phosphate, 10 to 30 milligrams, acetophenetidin, 100 to 300 milligrams; antihistaminics, for example, chlorpheniramine maleate, 1 to 4 milligrams or pyrathiazine hydrochloride, 12.5 to 50 milligrams can be added to the composition of the instant invention. For allergic conditions particularly advantageous combination comprises a core of 6-methyl-prednisolone 0.5 milligram, calcium carbonate, 200 milligrams, and chlorpheniramine maleate, 2 milligrams; the outer coat contains 300 milligrams of acetylsalicylic acid. In arthritic or rheumatic conditions, especially good results are obtained from combination of 6-methyl-prednisolone, 0.3 to 1.5 milligrams and

calcium carbonate, 200 milligrams in the core while the outer coat contains acetylsalicylic acid 300 milligrams and meprobamate 100 to 200 milligrams.

Various secondary ingredients can be added to the composition of the instant invention. These secondary ingredients include disintegrators, for example, corn starch and potato starch; lubricants, for example, mineral oil and calcium stearate; diluents, for example, talc and sucrose; and binders, for example, methylcellulose and starch paste. Certified dyes can be used in the tablet core and in the outer coat.

The composition of the instant invention is useful in inflammatory and rheumatic afflictions susceptible to oral treatment and counteracts the gastric distress often associated with salicylate and adrenocortical steroid hormone therapy.

The first attempts to prepare a satisfactory pharmaceutical composition containing acetylsalicylic acid, buffer and adrenocortical steroid utilized the conventional technique of simple admixture of the various powdered ingredients. It was thought that an admixture of this type could be used as a bulk powder or filled into a telescoping capsule. It was discovered that such an admixture of powders was highly unstable. When placed in closed bottles or in capsules, the admixture developed a strong acetic acid odor and a distinct pink coloration. The U.S.P. permissible limits of acetylsalicylic acid hydrolysis were greatly exceeded. Moreover, a build up of gas pressure was found to occur in closed containers and in capsules containing the admixture.

Additional attempts to prepare a satisfactory pharmaceutical composition containing the three above types of active ingredients led to the preparation of a conventional compressed tablet. The difficulties and stability problems encountered with a simple powder admixture, as outlined above, were still present and in fact increased in that the steroid component deteriorated rapidly at 47° centigrade, as shown in Table I.

TABLE I

Steroid Stability	Tablet Number 1167
Assay — Initial	0.525 milligram per tablet
at 1 month	0.411 milligram per tablet
at 3 months	0.332 milligram per tablet

The result was checked by a more accelerated stability test run at 70 degrees centigrade. After two days the initial content of the steroid of 1.5 milligrams per tablet had deteriorated to the level of only 0.55 milligram per tablet, showing that a storage-stable composition had not been obtained.

The failure of the recited attempts to prepare the subject composition in stable form led to the concept that interaction of the ingredients was causing the instabilities and that a novel method must be found for including the active ingredients in a single dosage form but at the same time preventing interaction by physical separation. Attempts were therefore made to utilize the technique hereinbefore defined as compression-coating. Numerous experimental procedures were followed in an endeavor to obtain maximum stability, satisfactory bonding and optimum ratio of active ingredients consistent with a pharmaceutically elegant and size-acceptable ultimate tablet. All procedures failed to meet one or more of the desiderata until the composition and process of the invention were developed. Among the numerous experimental procedures the following are typical.

SERIES A

The tablet core contained prednisolone (1.5 milligrams) coated with ethylcellulose. The compression-coat was applied by compressing on the tablet core a mixture of an acetylsalicylic acid (300 milligrams) granulation and an aluminum hydroxide (135 milligrams)—magnesium trisilicate (65 milligrams) granulation.

The bonding action of the core and coat was insufficient to guarantee a physically stable ultimate tablet. The ultimate tablet was too large for pharmaceutical elegance.

Reduction of the size of the ultimate tablet to satisfy pharmaceutical elegance failed in view of the continued absence of reciprocal bonding action between the tablet core and the compression coat.

SERIES B

The tablet core contained 1.5 milligrams of presdnisolone. The compression-coat was applied by compressing on the tablet core a mixture of an acetylsalicylic acid (300 milligrams) granulation and a calcium carbonate (100 milligrams)—magnesium oxide (100 milligrams) granulation.

The ultimate tablet was unsatisfactory be-

cause of excessive hydrolysis of the acetylsalicylic acid and deterioration of the adrenocortical steroid.

Coating of the tablet core with ethylcellulose did not improve sufficiently the acetylsalicylic acid stability.

SERIES C

The tablet core contained 1.5 milligrams of prednisolone, and acetylsalicylic acid. Only 150 milligrams of acetylsalicylic acid could be included in the tablet core for compression-coating with a buffer mixture containing 150 milligrams of calcium carbonate and 150 milligrams of magnesium oxide. Increasing the acetylsalicylic acid to the required level of 300 milligrams and then applying the compression coat gave a tablet too large for pharmaceutical acceptability. Moreover, an ultimate tablet with only 150 milligrams of acetylsalicylic acid impaired the proper steroid-analgesic ratio.

SERIES D

The tablet core contained 1.5 milligrams of prednisolone. The compression coat was applied by compressing on the tablet core a mixture of an acetylsalicylic acid (300 milligrams) granulation and a calcium carbonate (200 milligrams) granulation. The gross appearance appeared satisfactorily but the bonding action between the tablet core and the compression-coat was unsatisfactory.

Coating of the tablet core with ethylcellulose did not improve the bonding action sufficiently to guarantee physical stability.

SERIES E

An attempt was made to prepare a tablet core of prednisolone (1.5 milligrams) and acetylsalicylic acid (300 milligrams) with a compression-coat of calcium carbonate (200 milligrams). However, only 162 milligrams of acetylsalicylic acid could be incorporated with the prednisolone in said tablet core because of greatly increased core dimensions with the full 300 milligrams. It required about 400 milligrams of calcium carbonate to complete the ultimate tablet, thereby rendering inoperative the buffer to acetylsalicylic acid ratio.

SERIES F

The tablet core contained 1.5 milligrams of prednisolone. The compression-coat contained acetylsalicylic acid (240 milligrams) and aluminum hydroxide (160 milligrams). In addition to excessive acetylsalicylic acid hydrolysis the ultimate tablet was unsatisfactory in not possessing the required bonding action between the tablet core and the compression-coat.

Although the tablet core was coated with ethylcellulose and the compression-coat applied as outlined the required bonding action between the core and coat was not obtained.

SERIES G

The tablet core contained calcium carbonate (200 milligrams). The compression-coat contained 1.5 milligrams of prednisolone and acetylsalicylic acid (300 milligrams). Although the bonding action of the core and the coat was satisfactory, excessive hydrolysis of the acetylsalicylic acid occurred accompanied by deterioration of the adrenocortical steroid.

SERIES H

The tablet core contained 1.5 milligrams of prednisolone and calcium carbonate (200 milligrams). The compression-coat contained acetylsalicylic acid (300 milligrams). The ultimate tablet appeared to be satisfactory by all criteria until deterioration of the prednisolone was detected. This deterioration led to the discovery that the method of preparation of the prednisolone and calcium carbonate was critical. The technique of granulating the adrenocortical steroid with the calcium carbonate, which is optimum from manufacturing considerations, resulted in an ultimate tablet subject to steroid deterioration. However, adding the prednisolone as a powder to previously granulated calcium carbonate resulted in an ultimate tablet meeting all the stability and pharmaceutical criteria.

The following examples are illustrative of the processes and products of this invention, and are not to be construed as limiting.

EXAMPLE 1

Preparation of Tablet Cores

Each core contains:

	Mixture Part I
200 milligrams	Calcium carbonate USP dense, bolted
	Paste for granulating Part I
	Starch bolted 1 part
	Syrup 50 percent 3 parts
	Deionized water 6 parts
	Mixture Part II
0.5 milligram	Prednisolone
6.0 milligrams	Starch bolted
9.0 milligrams	Talc bolted
	Lubrication
1.6 milligrams	White mineral oil USP, viscosity 180
Directions:	The Mixture Part I is granulated with q.s. starch-syrup paste and dried at 140 to 180 degrees Fahrenheit for twenty hours. The prednisolone is bolted with some of the starch through number 9 cloth (100 mesh) and mixed with the balance of the starch and talc. The mineral oil is sprayed on the dried granulated Part I in a lubricating tub. The Mixture Part II is added and the whole stirred well. The lubricated mixture of Part I and Part II is slugged and the slugs broken up by forcing through a number 12 screen. The screened material is restirred in the lubricating tub and compressed into the tablet cores. All processing is carried out at a relative humidity of less than about forty percent.

EXAMPLE 1—continued

Preparation of Compression-Coated Tablets

Each tablet contains:

	Part I
one	Tablet core
	Part II
300 milligrams	Acetylsalicylic acid
	Add to Part II for Lubricating
24 milligrams	Talc bolted
6 milligrams	Starch bolted
9 milligrams	Certified dye
Directions:	Blend Part II in a lubricating tub. Then slug Part II and mill the slugs through a Fitz mill using 0.093 screen. Form the compression-coat on the core in the compression-coating machine. Maintain a relative humidity of less than forty percent during all processing steps.

These compression-coated tablets are assayed for moisture, calcium carbonate, prednisolone and acetylsalicylic acid, and used clinically with satisfactory results.

EXAMPLE 2

Using the procedure of example 1, compression-coated tablets are prepared containing 0.5 milligrams of prednisolone per tablet in place of the 1.5 milligrams of example 1. These tablets are assayed for moisture, calcium carbonate, prednisolone and acetylsalicylic acid, and used clinically with satisfactory results.

EXAMPLE 3

Using the procedure of example 1, the compression-coated tablets are prepared with a compression-coat containing from 200 to 400 milligrams of acetylsalicylic acid, and a tablet core containing from 0.25 to 5 milligrams of prednisolone and 100 milligrams of calcium carbonate in excess of the amount equimolar with said acetylsalicylic acid.

EXAMPLE 4

Following the procedure of example 1, compression-coated tablets are prepared from a tablet core containing, in place of the prednisolone of example 1, cortisone acetate from 2.5 to 25 milligrams; hydrocortisone acetate, from 2 to 20 milligrams; prednisone, from 0.25 to 5.0 milligrams; 6-methyl-prednisolone, from 0.15 to 4 milligrams; 6-fluorohydrocortisone, from 0.15 to 4 milligrams; and 6-fluoroprednisolone, from 0.15 to 4 milligrams.

EXAMPLE 5

Following the procedure of example 1, except for the substitution of the acetylsalicylic acid by [acetylsalicylic acid]-anhydride, compression-coated tablets are prepared from a core containing 1.5 milligrams of prednisolone and 200 milligrams of calcium carbonate, with a coating of 300 milligrams of [acetylsalicylic acid]-anhydride. The latter compound yields acetylsalicylic acid on gradual hydrolysis.

EXAMPLE 6

Following the procedure of example 1, except for the substitution of prednisolone by 6 - methyl - prednisolone, compression-coated tablets are prepared, each containing 0.35 milligram of 6-methyl-prednisolone and 1.0 milligram of 6-methyl-prednisolone, respectively. These tablets are assayed for strength of the active ingredients and used clinically with satisfactory results.

EXAMPLE 7

The acetylsalicylic acid of the respective products of example 6 is substituted by [acetylsalicylic acid]-anhydride to prepare compression-coated tablets containing an outer coat of said anhydride and a core section containing a mixture of calcium carbonate and 6-methyl-prednisolone.

Comparative tests show the composition of

this invention to be superior to similar compositions heretofore available commercially. Tests on adrenocortical steroid stability, acetylsalicylic acid hydrolysis, gas formation, and acid neutralization were performed. The results of these tests are tabulated below.

Table I contains the data on steroid content from comparative stability tests run at 70° centigrade.

TABLE I

Time	A	B	C	D
Start	100%	100%	100%	100%
20 hours	97%	94%	95%	94%
40 hours	94%	90%	89%	88%
60 hours	90%	81%	77%	78%
80 hours	87%	72%	64%	65%

These data show the marked superiority of A, i.e., the composition of the invention, over B, C, and D, i.e., other similar commercially available products.

Table II contains the data on acetylsalicylic acid hydrolysis from comparative, accelerated tests run on four products at 70 degrees centigrade in sealed containers.

TABLE II

Time	A—1	B—1	A—2	B—2
Start	0.0%	3.5%	0.0%	3.5%
20 hours	0.6%	8.0%	1.7%	7.9%
40 hours	1.7%	12.0%	8.0%	12.0%
60 hours	5.0%	18.0%	15.0%	18.0%

These data show that A—1 and A—2, i.e., the compositions of the invention are significantly more resistant to acetylsalicylic acid hydrolysis than B—1 and B—2, i.e., other similar commercially available products.

Table III contains the data from tests on gas formation from seven compression-coated tablets of each of two products stored at seventy degrees centigrade in sealed containers.

TABLE III

Time	A	B
Start	0	0
20 hours	0	0.5 cc.
40 hours	0.2 cc.	2.5 cc.

These data show the significantly slower gas production, from deterioration of the ingredients in product A, i.e., the composition of the invention, than in product B, a similar commercially available product. It should be noted that the *first* appearance of gas formation is indicative of ingredient deterioration.

Table IV contains the comparative data on

pH titration of whole compression-coated tablets by the method of Dale and Booth, J. A. Ph. Assoc., Sci. Ed., 44 page 170, 1955. In this method one whole tablet is tested in simulated gastric juice (pH 10) at 37 degrees centigrade.

TABLE IV

Time	A	B	C
Start	pH 1.0	pH 1.0	pH 1.0
3 minutes	pH 1.6	pH 1.0	pH 1.03
10 minutes	pH 1.8	pH 1.02	pH 1.1
20 minutes	pH 1.35	pH 0.95	pH 1.1
30 minutes	pH 1.15	pH 0.9	pH 1.0

These data show that product A, i.e., the composition of the invention possesses faster and superior buffering power to products B and C, i.e., other similar commercially available products.

Although the composition and method of the instant invention provide a compression-coated tablet which is not subject to excessive deterioration of the active ingredients and is pharmaceutically acceptable judged by the criteria of elegance and size, it is preferred to maintain the moisture content of the ultimate compression coated tablet below a specified percent. The practical manufacturing methods of granulating, mixing, and compressing are such that the introduction of excessive moisture is an ever-present danger. Consequently, precautions to maintain low relative humidity atmospheric conditions are preferred and ingredients relatively free from moisture are preferred.

The experimental results showed that a moisture content per ultimate tablet of less than 0.9 percent prevented excessive deterioration of the active ingredients including the adrenocortical steroid hormone which formed an etioacid degradation product.

WHAT WE CLAIM IS:—

1. A medicinal tablet comprising a compression-coated outer layer containing acetylsalicylic acid or a non-toxic compound convertible to acetylsalicylic acid on hydrolysis and an inner core bonded to said outer layer containing a mixture of an adrenocortical steroid and calcium carbonate.

2. A medicinal tablet as claimed in claim 1 wherein the adrenocortical steroid is cortisone, hydrocortisone, prednisone, prednisolone, 6-methyl-prednisolone, 6-fluoro-hydrocortisone, 6-fluoro-prednisolone or the therapeutically active derivatives thereof.

3. A medicinal tablet as claimed in claim 1 or 2 wherein the outer layer contains acetylsalicylic acid and the steroid used is prednisolone.

4. A medicinal tablet as claimed in claim 1 or 2 wherein the outer layer contains [acetylsalicylic acid]-anhydride and the steroid used is prednisolone.

5. A medicinal tablet as claimed in claim 3 wherein 200 to 400 milligrams of acetylsalicyclic acid, 0.25 to 5.0 milligrams of prednisolone and an amount of calcium carbonate, about 100 milligrams in excess of the amount equimolar with the acetylsalicyclic acid.

6. A medicinal tablet as claimed in claim 3 or 4 wherein 300 milligrams of acetylsalicylic acid or [acetylsalicylic acid]-anhydride, 1.5 milligrams of prednisolone and 200 milligrams of calcium carbonate is present.

7. A medicinal tablet as claimed in claim 1 wherein the outer layer contains acetylsalicylic acid or [acetylsalicylic acid]-anhydride and the water content of the tablet is less than 0.9% by weight.

8. A medicinal tablet as claimed in claim 7 wherein 300 milligrams of acetylsalicylic acid, 0.5 milligrams of prednisolone and 200 milligrams of calcium carbonate is present.

9. A medicinal tablet as claimed in claim 7 wherein 300 milligrams of acetylsalicylic acid 0.35 milligrams of 6-methyl-prednisolone and 200 milligrams of calcium carbonate is present.

10. A medicinal tablet as claimed in claim 7 wherein 300 milligrams of [acetylsalicylic acid]-anhydride 1.0 milligrams of 6-methyl-prednisolone and 200 milligrams of calcium carbonate is present.

11. A process of preparing a compression-coated tablet containing an adrenocortical steroid, calcium carbonate and acetylsalicylic acid or a non-toxic compound capable of yielding acetylsalicylic acid on hydrolysis which process comprises mixing an adreno-

cortical steroid with a granulation of calcium carbonate, compressing the said steroid-calcium carbonate mixture to form a core section and compression-coating a bonded layer of acetylsalicylic acid or a non-toxic compound yielding acetylsalicylic on hydrolysis, on said core section.

12. A process as claimed in claim 11 characterised in that said process is carried out under a low relative humidity and with ingredients sufficiently dry to produce a tablet having a moisture content of less than 0.9 percent by weight.

13. A process for the preparation of a medicinal tablet substantially as herein described with reference to any of the examples.

14. A medicinal tablet as claimed in any of claims 1 to 10 when prepared by a process as claimed in any of claims 11 to 13.

For the Applicants:—
GILL, JENNINGS & EVERY,
Chartered Patent Agents,
51/52 Chancery Lane, London, W.C.2.

Leamington Spa: Printed for Her Majesty's Stationery Office, by the Courier Press.—1961.
Published by The Patent Office, 25, Southampton Buildings, London, W.C.2, from which copies may be obtained.